

## Genetic and Molecular Insights Linking Mood Disorders and Pain

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### Abstract

Pain has been a constant companion of humankind since the dawn of time. As a sensory perception, it is a complex, multidimensional phenomenon and an integral part of human life. It is always a personal experience influenced by numerous endogenous and exogenous factors. Since pain is an unpleasant sensation, it is always associated with an emotional component. In addition to being personal, it is also a multifaceted experience, and its perception and awareness change throughout a person's life. Pain can lead to impulsive behavior, affecting decision-making and self-control.

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As a universal and complex phenomenon in the animal world, it has fascinated scientists, clinicians, and philosophers for centuries. It goes beyond simple sensory perception and encompasses a multidimensional experience that includes not only the recognition of harmful stimuli but also cognitive and behavioural responses. This multifaceted nature of pain makes it a subject of great interest and research in various fields, including neurology, psychology, and clinical medicine.

**Keywords:** pain, mood disorders, arthritis, biomarkers

## 1. Introduction

Pain and mood disorders frequently share common biological pathways, and an increasing body of evidence points to specific genetic factors and biomarkers that may underlie this overlap. In clinical practice and research, significant efforts are directed toward identifying specific determinants that link these two conditions, as their elucidation could open new avenues for therapeutic development [1].

Advances in genetics have revealed that subtle variations in genes encoding receptors and signaling molecules may partially explain interindividual variability in pain sensitivity, perception, and expression [2]. These variations may, in turn, influence how pain is treated and managed [3]. Several genetic markers and potential epitopes have been identified as critical contributors to both pain dysregulation and mood disorders.

## 2. Materials and Methods

In accordance with the principles of high-quality narrative reviews [4], we conducted a structured and comprehensive literature search to synthesize current available data on genetic and epigenetic insights that are linked in pain and mood disorders.

### 2.1 Databases and sources

To ensure a multi-disciplinary perspective (encompassing rheumatology, gastroenterology, pathology, and radiology), we systematically searched the following electronic databases: PubMed/MEDLINE, Web of Science, DynaMed, and Scopus. These platforms were selected to capture high-impact articles, reviews and meta-analyses and recent preprints. The reference lists of key articles and previous systematic reviews were manually screened to ensure no seminal works were omitted.

## 2.2 Search Terms and strategy

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The Boolean logic was tailored to each database's syntax to maximize sensitivity and specificity. The primary string used was: ("pain" OR "pain syndromes in rheumatology" OR "rheumatic pain") AND ("mood disorders" OR "depression and anxiety" AND ("genetic" OR "epigenetic" OR "mechanism" OR "insights")). The search was iterative, allowing for the inclusion of specific cytokines and gene epitopes which are relevant to the systemic overview.

## 2.3 Criteria

Articles were considered eligible if they addressed the link between the two topics. We prioritized: high-quality reviews and meta-analyses, case series providing novel insights into rare manifestations or refractory cases, original prospective and retrospective research articles. We excluded studies focusing on isolated disease, technical laboratory reports without clinical validation, editorials, letters, and abstracts lacking sufficient methodology, articles published in languages other than English (to ensure consistency in terminology and peer-review standards).

To capture the most contemporary advancements, we focused the search on publications from 1995 to 2025. This timeframe aligns with the modern recognition of the link of the topics. Findings were summarized thematically.

## 3. Genetic and epigenetic markers linked to pain and mood disorders

### 3.1 Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which also includes nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Early research on neuronal synthesis, secretion, and release of BDNF, as well as its interaction with the high-affinity receptor tropomyosin receptor kinase B (TrkB), was primarily conducted in the hippocampus, neocortex, and basal forebrain - regions essential for higher cognitive functions. However, neurotrophin synthesis and processing follow similar pathways in both central and peripheral neurons involved in nociceptive processing.

BDNF is present in human blood, although it is more highly concentrated in brain tissue. It has been suggested that BDNF can cross the blood-brain

barrier (Pan et al., 1998), and that its levels in the brain and serum undergo similar changes during maturation and aging. This suggests that serum BDNF levels may reflect central nervous system concentrations.

BDNF plays a crucial role in neuronal growth and survival and is implicated in both mood disorders (e.g., depression) and pain modulation [5, 6, 7]. It is increasingly recognized as a key regulator of synaptic plasticity, functioning both as a neurotransmitter and neuromodulator [8]. Furthermore, BDNF is a central molecule in neuroscience and neurobiology, contributing to neuronal differentiation, development, maintenance, and neuroprotection, as well as neurodegeneration and mood regulation [9, 10].

Genetic variability in BDNF is of particular importance [11, 12, 13]. The Val66Met polymorphism is among the most extensively studied variants; the Met allele has been associated with increased risk of depression and altered pain perception, particularly in chronic pain conditions. Additionally, the BDNF 196G/A polymorphism has been associated with geriatric depression in Chinese populations [14] and with Alzheimer's disease-related depression in Italian populations [15]. Licinio et al. reported that six single nucleotide polymorphisms (SNPs) in the BDNF gene (rs12273539, rs11030103, rs6265, rs28722151, rs41282918, rs11030101) are associated with mood disorders, with two haplotypes showing significant associations with depression [16]. Notably, a polymorphism in the 5' untranslated region (rs61888800) has been linked to treatment response.

Alterations in BDNF levels have been observed in individuals with both chronic pain [17] and mood disorders [18], suggesting a shared pathophysiological mechanism. Reduced BDNF levels are consistently reported in patients with depression and are negatively correlated with disease severity [19]. Moreover, stress has been shown to decrease BDNF expression, implicating it in the pathophysiology of anxiety disorders as well [20].

Under physiological conditions, BDNF is synthesized by various neuronal and glial cell types within pain pathways. Noxious stimuli can induce its production and release, contributing to synaptic plasticity and increased responsiveness of peripheral nociceptors. This sensitization may occur at both peripheral and central levels. Inflammatory processes are often associated with increased BDNF release as part of complex signaling cascades, exerting both neuroprotective and detrimental effects depending on the context [21]. Similarly, peripheral nerve injury leading to neuropathic pain is associated with upregulation of BDNF.

Understanding the role of BDNF holds significant promise for improving diagnosis and treatment of both pain and mood disorders. In nociception, it may inform novel strategies for chronic pain management. Three main therapeutic approaches targeting BDNF/TrkB signaling have emerged from preclinical studies: BDNF sequestration, blockade of the extracellular TrkB domain, and inhibition of the intracellular kinase domain. Although promising, these approaches are not yet ready for clinical application.

BDNF is also deeply involved in glutamatergic neurotransmission [22], which itself plays a critical role in mood disorders. Therefore, investigating correlations between BDNF (or proBDNF) and glutamate-related compounds may yield valuable biomarkers and therapeutic targets.

### 3.2. COMT – Catechol-O-methyltransferase

The metabolism of catecholamines is regulated by several enzymes, among which catechol-O-methyltransferase (COMT) plays a central role. In humans, COMT is encoded by the *COMT* gene and, together with voltage-gated sodium channels, contributes significantly to pain perception and processing [23, 24]. The gene is located on chromosome 22q11.2 and contains a well-characterized G-to-A missense single nucleotide polymorphism (SNP), resulting in the substitution of valine (Val) with methionine (Met) at codon 158 [25, 26].

COMT exists in two primary isoforms: membrane-bound (MB-COMT) and soluble (S-COMT) [25]. Functionally, COMT is primarily involved in the degradation of catecholamines such as dopamine and norepinephrine, thereby playing a crucial regulatory role in both mood regulation and pain processing.

Several genetic variations influence COMT enzymatic activity, among which the Val158Met polymorphism (rs4680) is particularly significant. This nonsynonymous SNP leads to a Val→Met substitution, resulting in a three- to fourfold reduction in enzymatic activity [27]. Consequently, this polymorphism directly modulates dopamine metabolism. Reduced COMT activity alters dopaminergic neurotransmission, leading to decreased endogenous enkephalin levels and increased pain sensitivity. Simultaneously, altered dopamine levels are associated with an increased risk of mood disorders, including depression. COMT is especially critical in the prefrontal cortex, where it accounts for approximately 60% of dopamine catabolism [28].

Notably, the Met allele exhibits approximately 40% lower enzymatic activity compared to the Val allele, which influences synaptic dopamine

availability [29]. COMT effects are predominantly cortical, particularly within the prefrontal cortex [30], but also extend to other brain regions such as the striatum and its functional interaction with the prefrontal cortex [31]. Furthermore, COMT modulates orbitofrontal–amygdala connectivity in response to negative emotional stimuli [32]. Sex differences have also been reported, with higher COMT activity observed in females, potentially due to estrogen-mediated transcriptional regulation [33].

Overall, evidence suggests that different COMT alleles are associated with distinct clinical phenotypes. The Val allele has been linked to certain mood-related traits and may contribute to increased pain sensitivity, highlighting the gene's role in the shared neurobiology of pain and affective disorders [34].

### 3.3. OPRM1 – $\mu$ -Opioid Receptor Gene

The endogenous opioid system plays a fundamental role in pain modulation, emotional regulation, reward processing, and substance use disorders. The *OPRM1* gene encodes the  $\mu$ -opioid receptor (MOR), a key mediator of analgesia and affective processing. MORs are widely distributed throughout the brain, with particularly high expression in the thalamus, limbic system (including the amygdala), nucleus accumbens, and anterior cingulate cortex [35]. Genetic variation within *OPRM1* significantly influences receptor function.

A well-studied functional SNP, A118G (rs1799971), results in an amino acid substitution (Asn40Asp) within exon 1, affecting receptor glycosylation and function [36]. Carriers of the G allele exhibit reduced baseline  $\mu$ -opioid receptor availability in brain regions associated with pain and emotional regulation. This polymorphism has been linked to altered pain perception, increased pain sensitivity, and heightened vulnerability to depression and anxiety [37]. G allele carriers not only experience pain more intensely but also rate it as more severe.

The opioid system also plays a role in sleep regulation. Opioid activity can reduce adenosine levels in the pontine reticular formation via  $\mu$ 1-opioid receptor activation, leading to dose-dependent sleep disturbances [38]. Variations in *OPRM1* may therefore contribute to individual differences in both analgesic response and sleep-related side effects [39].

In summary, individuals carrying the G allele may be more susceptible to both pain and mood disturbances due to altered opioid system functioning.

### 3.4. TNF- $\alpha$ – Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF- $\alpha$ ) is a pro-inflammatory cytokine that plays a critical role in the inflammatory response. Inflammation has been strongly implicated in both chronic pain and mood disorders, particularly depression.

Elevated levels of TNF- $\alpha$  have been consistently observed in individuals with chronic pain and depressive disorders. Initial reports linking increased TNF- $\alpha$  levels to depression date back to 2000 [40]. Subsequent studies have demonstrated correlations between circulating TNF- $\alpha$  levels and the severity of depressive symptoms, as well as normalization following antidepressant treatment [41]. Pro-inflammatory cytokines are also associated with increased pain sensitivity [42]. For example, patients with neuropathic pain exhibit elevated mRNA levels of TNF- $\alpha$  and IL-2, alongside reduced levels of the anti-inflammatory cytokine IL-10 [43].

The TNF- $\alpha$  gene contains a functional polymorphism at position -308 (G $\rightarrow$ A), which affects gene transcription. The A allele is associated with increased TNF- $\alpha$  production [44], contributing to an enhanced inflammatory response [45]. Importantly, this polymorphism has been linked to depression. Individuals carrying the A allele show a higher prevalence of depressive disorders, including early-onset depression [46].

These findings suggest that inflammation may represent a shared biological mechanism underlying both pain and mood dysregulation.

### 3.5 HTTLPR – Serotonin Transporter-Linked Polymorphic Region

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter involved in regulating sleep, appetite, vascular tone, platelet function, motor activity, and pain [47, 48]. However, it is most widely recognized for its role in mood and behavior regulation [49, 50].

The serotonin transporter (5-HTT), encoded by the *SLC6A4* gene, is responsible for the reuptake of serotonin from the synaptic cleft, thereby terminating serotonergic signaling [51]. A polymorphism in the promoter region of this gene, known as 5-HTTLPR, results in two main alleles: short (S) and long (L). The S allele is associated with reduced transcriptional efficiency, leading to decreased transporter expression and impaired serotonin reuptake [52]. This results in altered serotonergic signaling. The S allele has been consistently associated with increased vulnerability to depression, anxiety, and pain-related conditions such as fibromyalgia and

tension-type headaches [53]. Additionally, S allele carriers exhibit higher levels of neuroticism, a personality trait linked to emotional instability [54].

Neuroimaging studies show that S allele carriers exhibit heightened amygdala reactivity to emotional stimuli, suggesting increased emotional sensitivity [55]. This may result from altered top-down regulation from the prefrontal cortex, affecting emotional processing circuits [56, 57]. Furthermore, the 5-HTTLPR polymorphism influences treatment response. Individuals homozygous for the L allele tend to respond better to selective serotonin reuptake inhibitors (SSRIs) compared to S allele carriers [58, 59].

Overall, this polymorphism plays a crucial role in both emotional regulation and pain modulation, supporting its relevance in the comorbidity of pain and mood disorders [60, 61, 63-65].

### **3.6. CACNA1C – Voltage-Gated Calcium Channel Subunit Alpha-1C**

The *CACNA1C* gene encodes the  $\alpha 1C$  subunit of the Cav1.2 L-type voltage-gated calcium channel, which is essential for neuronal excitability, neurotransmitter release, and synaptic plasticity [66].

Cav1.2 channels are widely expressed in the brain and are involved in linking membrane depolarization to intracellular calcium signaling [67]. This process influences gene transcription, neuronal survival, dendritic development, learning, and memory [68, 69]. Genetic variations in *CACNA1C* have been associated with psychiatric disorders, including bipolar disorder, major depressive disorder, and anxiety [70, 71]. These variations have also been linked to pain conditions such as chronic pain and fibromyalgia [72, 73]. The overlap in genetic susceptibility suggests a shared mechanism involving calcium signaling dysregulation and neuronal hyperexcitability [74-77].

### **3.7. SCN9A – Voltage-Gated Sodium Channel**

The *SCN9A* gene encodes the Nav1.7 sodium channel, which plays a crucial role in pain signal transmission [78]. These channels are expressed in sensory neurons, particularly in dorsal root ganglia [79]. Mutations in *SCN9A* can result in either loss or gain of function. Loss-of-function mutations lead to congenital insensitivity to pain, whereas gain-of-function mutations are associated with severe pain disorders such as erythromelalgia and small fiber neuropathy [80, 81].

Polymorphisms such as rs6746030 have been linked to increased pain sensitivity and chronic pain severity [82-84]. Altered sodium channel

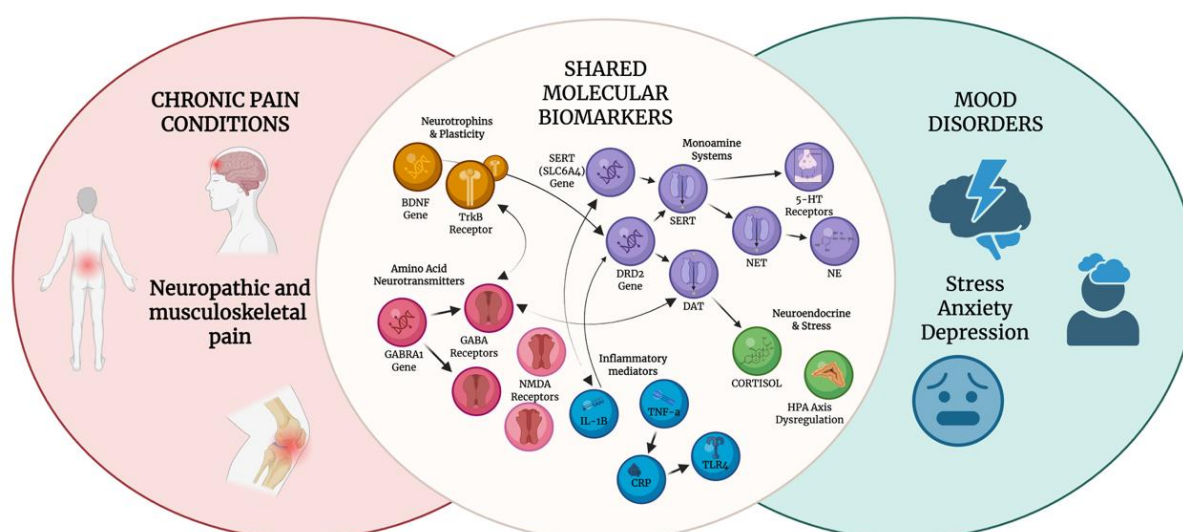
function may also contribute to mood dysregulation through its effects on neural signaling.

### 3.8. HPA Axis and Glucocorticoid Receptor (NR3C1)

The hypothalamic–pituitary–adrenal (HPA) axis regulates the stress response, and its dysregulation is strongly associated with both mood disorders and chronic pain. The *NR3C1* gene encodes the glucocorticoid receptor (GR), which mediates the effects of cortisol [85]. Alterations in GR function can disrupt HPA axis feedback mechanisms, leading to abnormal stress responses. Patients with mood disorders often exhibit HPA axis hyperactivity, including elevated cortisol levels and impaired dexamethasone suppression [86, 87]. Chronic stress induces structural and functional brain changes, including reduced neurogenesis and altered serotonin metabolism [88].

Variations in *NR3C1* may influence receptor sensitivity and stress reactivity, contributing to both emotional dysregulation and pain hypersensitivity [89].

The intricate relationships between the various genes and epitopes described above are illustrated in Figure 1, highlighting their intersection across both clinical domains.



**Figure 1.** Shared Molecular Pathways and Biomarkers in Chronic Pain and Mood Disorders.

Abbreviations: BDNF, Brain-derived neurotrophic factor; TrkB, Tropomyosin receptor kinase B; SERT, Serotonin transporter; SLC6A4, Serotonin transporter gene; 5-HT, 5-hydroxytryptamine (Serotonin); DRD2, Dopamine receptor D2; DAT, Dopamine transporter; NET, Norepinephrine transporter; NE, Norepinephrine; GABRA1, Gamma-aminobutyric acid type A receptor alpha 1 subunit gene; GABA, Gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; IL-1B, Interleukin-1 beta; TNF- $\alpha$ , Tumor necrosis factor alpha; CRP, C-reactive protein; TLR4, Toll-like receptor 4; HPA, Hypothalamic–pituitary–adrenal.

#### 4. Discussion

The present synthesis highlights that the comorbidity between chronic pain and mood disorders is best conceptualized as a shared neurobiological continuum rather than a co-occurrence of distinct clinical entities. Across genetic, epigenetic, and molecular levels, converging evidence supports the involvement of partially overlapping pathways regulating neuroplasticity, monoaminergic transmission, immune activation, and stress responsivity. However, the overall picture remains complex, with substantial heterogeneity in findings and limited translational consistency.

Among the most consistently implicated mechanisms is dysregulation of neuroplasticity-related signaling, particularly involving *BDNF*. Reduced *BDNF* expression has been associated with both depressive symptom severity and enhanced central sensitization in chronic pain states, supporting the hypothesis that impaired synaptic plasticity represents a shared biological substrate [17-20]. This aligns with the neurotrophic hypothesis of depression and extends its relevance to nociceptive processing. Similarly, alterations in HPA axis regulation, particularly via *NR3C1*-mediated glucocorticoid signaling, suggest that chronic stress exposure may act as a common upstream driver linking affective dysregulation and pain amplification [85].

Genetic variation in *COMT*, *SLC6A4* (5-HTTLPR), and *OPRM1* further reinforces the role of monoaminergic and opioid systems in the dual modulation of pain and mood [29,37,58]. However, a critical issue is the low replicability and small effect sizes of many candidate gene associations. For example, while *COMT Val158Met* has been widely studied, meta-analyses have demonstrated inconsistent associations across populations, suggesting that its functional relevance is likely context-dependent rather than deterministic [34]. This limitation reflects a broader methodological weakness in candidate gene research, particularly susceptibility to population stratification and publication bias.

Inflammatory signaling, particularly via TNF- $\alpha$  and related cytokine pathways, provides a more mechanistically robust link between pain and mood disorders [40-42]. Elevated pro-inflammatory cytokines have been observed in both conditions and are capable of inducing neurobehavioral changes through multiple pathways, including microglial activation, reduced monoamine availability, and altered glutamatergic transmission [90]. Importantly, inflammation may represent not only a consequence but also a causal amplifier of central sensitization and affective dysregulation, positioning it as a key therapeutic target. Nevertheless, heterogeneity in cytokine profiles across patient subgroups indicates that inflammation is unlikely to be a universal mechanism.

Variants in genes such as *CACNA1C* and *SCN9A* extend the discussion toward neuronal excitability and pain signal propagation. These genes underscore the importance of calcium and sodium channel regulation in shaping both sensory and affective processing networks [70-72, 80]. However, while their role in rare monogenic pain disorders is well established, their contribution to complex psychiatric and chronic pain phenotypes remains less clearly defined, with most evidence derived from association studies rather than functional validation.

A central limitation emerging from the literature is the dominance of the candidate gene approach, which has failed to fully capture the polygenic architecture of both pain and mood disorders. Many reported associations lack replication in genome-wide studies, reflecting the so-called “replication crisis” in psychiatric genetics [91]. In contrast, GWAS findings suggest highly polygenic risk profiles with individually small effect sizes distributed across hundreds of loci [92]. This discrepancy highlights a critical gap between early hypothesis-driven genetics and current systems-level genomic understanding.

An additional limitation of the current evidence base is the relatively superficial integration of epigenetic regulation and gene-environment interactions. Environmental stressors, early-life adversity, and chronic inflammation are increasingly recognized as key modulators of gene expression through DNA methylation, histone modification, and non-coding RNA activity [93]. These mechanisms may partially explain phenotypic divergence among individuals with similar genetic backgrounds. However, epigenetic studies in this field remain fragmented and lack longitudinal validation.

Despite these limitations, the convergence of multiple biological systems provides a rationale for mechanism-based stratification of patients rather

than symptom-based classification alone. Biomarkers derived from neurotrophic, inflammatory, and neuroendocrine pathways may ultimately enable more precise phenotyping of patients with overlapping pain and mood disorders [94]. Moreover, the partial efficacy of existing therapies targeting serotonergic, opioid, or inflammatory systems supports the notion of shared downstream pathways, even if upstream genetic drivers remain heterogeneous.

Future research should prioritize integrative multi-omics approaches, combining genomic, epigenomic, transcriptomic, and proteomic data within longitudinal clinical cohorts. Such strategies are essential to move beyond association-based frameworks toward predictive and mechanistic models. In parallel, standardized phenotyping of pain–mood comorbidity and harmonization of outcome measures will be necessary to improve reproducibility across studies. Ultimately, a shift toward systems biology and network-based psychiatry is required to fully elucidate the shared architecture of these conditions.

## 5. Strengths and limitations of the review

This review provides a timely and mechanistically oriented synthesis of genetic and epigenetic factors implicated in the shared pathophysiology of pain and mood disorders. Its principal strength lies in the integrative framework across molecular, neurobiological, and immunological domains, linking candidate gene variation (e.g., BDNF, COMT, OPRM1) with inflammatory signalling, ion channel dysfunction, and HPA axis dysregulation. By moving beyond single-pathway explanations, the manuscript appropriately reflects the current conceptual shift toward network-based and systems-level models of neuropsychiatric and pain comorbidity.

A further strength is the broad temporal scope of the literature base (1995–2025), which enables contextualization of early candidate gene findings alongside more recent mechanistic advances. The structured organization of genetic markers according to functional biological systems enhances conceptual clarity and supports translational interpretation. Importantly, the review also highlights clinically relevant convergence points, particularly neuroplasticity, immune signalling, and monoaminergic regulation, which are central to emerging precision medicine approaches.

However, several limitations constrain the interpretative strength and translational weight of the findings. First, despite the structured search strategy, the work remains a narrative synthesis without systematic

methodology, lacking formal study selection transparency, risk-of-bias assessment, and reproducibility of inclusion decisions. This inherently increases susceptibility to selection bias and author-dependent interpretation, particularly in a field characterized by heterogeneous and sometimes contradictory evidence.

Second, the review is largely anchored in the candidate gene paradigm, which has substantial limitations in the context of complex polygenic traits. Many highlighted associations (e.g., COMT Val158Met, 5-HTTLPR) have shown inconsistent replication across ethnic groups and study designs, reflecting well-documented issues of low effect sizes, population stratification, and publication bias in candidate gene research. Consequently, several mechanistic inferences should be interpreted as hypothesis-generating rather than confirmatory.

Third, there is limited integration of genome-wide association studies (GWAS), epigenome-wide data, and multi-omics approaches, which currently represent the most robust frameworks for understanding complex neuropsychiatric-pain overlap. The absence of these datasets partially restricts the manuscript's alignment with the most recent advances in psychiatric genetics and pain genomics. Finally, although the review acknowledges biological convergence, it underrepresents the critical role of gene-environment interactions, developmental influences, and psychosocial determinants, which are increasingly recognized as essential modifiers of both pain perception and affective vulnerability. This omission may overemphasize biological determinism in a clinically heterogeneous spectrum of disorders. In summary, while this review provides a coherent mechanistic synthesis of overlapping genetic pathways in pain and mood disorders, its conclusions should be interpreted within the constraints of narrative methodology and the inherent limitations of candidate gene evidence. Future high-impact research will require integration of multi-omics data, longitudinal cohort designs, and environment-stratified analyses to move from associative findings toward predictive and clinically actionable models.

## 6. Conclusions

Accumulating evidence supports a substantial biological convergence between chronic pain and mood disorders, underpinned by overlapping genetic, epigenetic, and neurobiological mechanisms. Rather than being independent clinical entities, these conditions increasingly appear to represent interconnected phenotypes within a shared dysregulated system,

involving neurotransmitter signaling, immune activation, synaptic plasticity, and stress-response pathways.

Key candidate genes, including *BDNF*, *COMT*, *OPRM1*, *TNF- $\alpha$* , *SLC6A4*, *CACNA1C*, *SCN9A*, and components of the HPA axis, collectively highlight the multisystem nature of vulnerability, where modest genetic effects converge on common downstream pathways such as altered monoaminergic transmission, neuroinflammation, and impaired neuroplasticity. Among these, the most consistently supported mechanisms involve dysregulation of neurotrophic signaling, particularly BDNF-mediated synaptic plasticity, and persistent low-grade inflammatory activation, which together may facilitate both central sensitization in pain and affective instability.

Importantly, current evidence indicates that the clinical overlap between pain and mood disorders cannot be sufficiently explained by single-gene effects. Instead, it reflects a polygenic and context-dependent architecture, in which genetic susceptibility interacts with environmental exposures, stress load, and developmental factors. This complexity is further compounded by inconsistent replication of candidate gene associations and the limited predictive value of individual polymorphisms across diverse populations. From a translational perspective, these insights reinforce the need to move beyond reductionist models toward integrated systems biology frameworks. Such approaches should incorporate genome-wide data, epigenetic regulation, transcriptomic signatures, and longitudinal clinical phenotyping to better capture disease heterogeneity and temporal dynamics. In parallel, identifying biologically meaningful endophenotypes - such as altered stress responsivity, neuroinflammatory profiles, or pain sensitization patterns - may provide more robust targets for stratified intervention.

Finally, the shared molecular pathways identified in this review provide a rationale for mechanism-based therapeutic strategies that simultaneously address affective and nociceptive dysregulation. However, the current evidence base remains largely associative, and significant gaps persist in establishing causality, clinical utility, and treatment predictability.

In conclusion, while substantial progress has been made in delineating the biological interface between pain and mood disorders, the field remains in a transitional phase. Future advances will depend on the integration of multi-omics approaches, well-characterized longitudinal cohorts, and gene-environment interaction models, ultimately enabling a shift from descriptive associations toward clinically actionable precision medicine frameworks.

## Declarations

### Author Contributions

Conceptualization: S.B.; Methodology: S.B.; Formal analysis: S.B, S.D.; Investigation: S.B; Writing – original draft: S.B.; Writing – review & editing: all authors.

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### Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

### Conflicts of Interest

The authors declare no conflict of interest.

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## **Генетични и молекулярни прозрения, свързващи афективните разстройства и болката**

### **Резюме**

Болката е постоянен спътник на човечеството от зората на времето. Като сетивно възприятие, тя представлява комплексен, многоизмерен феномен и неделима част от човешкия живот. Тя винаги е субективно преживяване, повлияно от множество ендогенни и екзогенни фактори. Тъй като болката е неприятно усещане, тя неизменно е свързана с емоционален компонент. Освен че е личен опит, тя е и многостранно преживяване, като нейното възприемане и осъзнаване се променят в хода на целия човешки живот. Болката може да доведе до импулсивно поведение, засягайки процесите на вземане на решения и самоконтрола. Като универсално и сложно явление в животинския свят, тя е обект на интерес за учени, клиницисти и философи в продължение на векове. Тя надхвърля рамките на обикновеното сетивно възприятие и обхваща многоизмерен опит, който включва не само разпознаването на вредни стимули, но и когнитивни и поведенчески реакции. Този многостранен характер на болката я превръща в обект на задълбочени изследвания в различни научни области, включително неврология, психология и клинична медицина.

**Ключови думи:** болка, афективни разстройства, артрит, биомаркери